A Possible Solution to the Etiological Paradox that Ties Anti-Social Personality Disorder to Major Depression

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Abstract: Antisocial personality disorder (ASPD) is a pervasive condition among youngsters around the globe, which has particular pungency in countries where the socioeconomic context favors delinquency. Several behavioral genetics studies have linked the disorder to the presence of copies of a polymorphic variation of the MAO-A gene that leads to enzymatic hypofunction. An emerging tendency in this literature is to also associate it to the presence of short variations of the 5-HTTLPR polymorphism, which is well-known for its possible role in the vulnerability to major depression of individuals that were exposed to early-life stress. The current paper argues that the association of these findings introduce a theoretical problem that is not trivial ("an apparent paradox"), and further proposes a solution to it.

Keywords **–** Antisocial Personality Disorder; Etiology; Behavioral Genetics; Major Depression; Endophenotypes.

INTRODUCTION: THE ETIOLOGICAL BASIS OF THE VULNERABILITY TO ANTISOCIAL DISORDER

Antisocial personality disorder (ASPD) is as psychiatric condition characterized by low empathy, low scores in moral tasks, morally deviant behaviors, with a high tendency toward deception, and violent tendencies [1, 2]; it is an "DSM-IV-R Axis 2" disorder that frequently emerges from earlier conduct disorders, present in childhood and adolescence. Due to its etiological approach, this paper will treat ASPD in conjunction with conduct disorders, under the general idea of a cluster of mental and behavioral tendencies that are socially inacceptable due to their social disservices.

Carriers of the disorder tend to have decreased that the capacity to prospect other people's intention (theory of mind) and to comprehend the deep senses involved in emphatic relations [3]. In terms of their affective style, carriers show a tendency toward offensive conducts; that is, in the light of the flight or fight dichotomy, they easily opt for the latter, which renders them impulsive and frequently destructive [4]. For a discussion on the affective styles in ASPD, see: [5].

Antisocial disorder is endemic among young offenders in several countries, although it is worth considering that the condition is not restricted to youngsters [6]. The main environmental variable associated to it is childhood victimization, which has been said to be a "significant predictor of the number of lifetime symptoms of antisocial personality disorder and of a diagnosis of antisocial personality disorder" [7] and believed to increase the risk of ASPD by about 50% [8], in what has been called the "cycle of violence" [9], alluding to the idea that those who suffer violence in their childhood tend to perpetrate it.

ASPD is also associated to other widespread cultural risk factors, such as drug abuse & addiction [10], and low social-economic conditions, which not only increases the vulnerability to the disorder but also worsen the cases, as revealed by a study focusing the demographic profile of Brazilian minor offenders, which revealed that most individuals did not have familial support and were not at school at the time of incarceration [11]. This picture contrasts with the one that is found in German [12], where the societal problem imposed by criminal minors is notable less severe.

In an epidemiological study, developed in collaboration with Dr. Daniel Martins de Barros and Dr. Antônio Serafim de Pádua (NUFOR-Ipq-FMUSP), which aimed to define the psychiatric profile of near one thousand incarcerated minors, we reached the conclusion that the most prevalent psychiatric condition in this cohort is antisocial personality disorder associated with the use of drugs (ICD-10: F10-19); at the same time, we found that certain psychiatric disorders tend to be less prevalent in this population and less related to re-incarceration than reported by previous international studies, focused on the psychiatric profile of young offenders from developed countries; i.e., [13]. Our study is under the final stage of peer-review in a well-known Journal.

For instance, Stefurak, Calhoun and Glaser [14] analyzed a database of more than one million diagnoses and reached the conclusion that the depression/anxiety cluster tends to be highly prevalent among these youngsters; we could not corroborate this conclusion in our study, regardless of the fact that depression rates are higher in the Brazilian population than they are in most developed countries, and of the fact that these rates vary in accordance to the local social

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demographic profile (e.g., rates of depression are higher in the less developed northeast part of the country, than in the southeast part; see: [15]).

Having said that, it is also important to bear in mind that several studies have provided evidences that genetic variables have an important place among the risk factors to the disorder. This is an old and well-known assumption, which entered the debate in the decade of 1970, by means of reports on the increased tendency toward violent, criminal behavior of men carrying the XYY aneuploidism [16].

Studies on the matter evolved significantly in relation to that era, first changing their focus from rare chromosomal aberrations and other rare genetic disorders to the additive role of common polymorphic variations that are widespread in the population, before reaching the current state of understanding of the biological basis of psychiatric disorders, which is broadly assumed as a scenario where rare mutations, chromosomal aberrations, epigenetic abnormalities, and additive polymorphisms represent different and yet convergent pathways to endophenotipic vulnerabilities, which lead to the consolidation of nosographic entities, in the presence of other contingent variables (biological and environmental).

When looking through the angle of the consolidation of endophenotipic vulnerabilities to different psychiatric disorders, predisposition to ASPD poses what I identify as an 'etiological paradox', which seems not to have been discussed in the specialized literature, in the terms that are presented in this paper (for different approaches, see: [17, 18]). In that sense, the aims of this paper are to present and to propose an evidence-based theoretical solution to it.

2. GENETIC RISK FACTORS TO ANTISOCIAL DISORDER

Currently, it is believed that the strongest genetic risk factor to antisocial disorder refers to the presence of variable number tandem repeat (VNTR) polymorphic copies of the gene MAO-A (located at the sexual chromosome Xp11.23-11.4), which are characterized by decreased tandem number (three instead of four 30bp tandem), in the transcriptional region of the gene. This variation diminishes the synthesis of the five hundred twenty seven amino acids MAO-A enzyme, which is chiefly involved in the degradation of biogenic amines, like the neurotransmitters dopamine, serotonin, and norepinephrine [19], thus leading to higher brain (synaptic) and serum availability of these monoamines.

The diminished enzymatic synthesis is the most notable endophenotipic trait linked to the vulnerability to the disorder (for a recent confirmation of this point, several times replicated, see: [20]). It is believed that it leads to higher intolerance to adverse interactions, in the context of past victimization [21]. The nature-nurture relation that is established seems to take place through impairments in the neurodevelopment of the limbic system (which is rendered increased in size) and amygdala hyper-responsivity [22], which affect inhibitory capacities and general affective stability.

That said, it is important to note that this is not the only polymorphism related to the disorder. Among the several other potential candidates to take place in the genetic landscapes of ASPD, it is becoming clear that a polymorphism of the serotonin transporter gene (SERT), which diminishes the serotonergic availability in several post-synaptic sites may be among the most important ones (for data and discussions, see: [23, 24]). This polymorphism of the SLC6A4 gene (located at the chromosome 17q12), is characterized by a microdeletion of 14-bp in a GC-rich region in the transcription part of the gene, and is popularly known as the short 5-HTTLPR variation (in fact it is one among several other polymorphic variations, with different lengths and functional performances). There is an emerging tendency on the literature to link this polymorphism to a possible serotonergic dysfunction that causes emotional deregulation in the disorder [25].

The short variation of the 5-HTTLPR is probably the most discussed polymorphism in biological psychiatry, due to its potential role in leading to major depression disorder (MDD), in contexts where the individual has suffered from childhood stress [26, 27]. Recently, the most rigorous genomic meta-analysis regarding the genetic risk factors to MDD pointed that presence of copies of this polymorphism represents the most consistent genetic risk factor to the disorder [28], while another recent meta-analysis confirmed the association between the presence of at least one copy of this variation, early stress, and proneness to depression [29].

The close ties between the nature-nurture vulnerability to ASPD and to MDD is escorted by a puzzling dichotomy, whose understanding this paper assumes to be crucial to both the proper understanding of the phenomenological structure of these two disorders and to the understanding of the effects brought by the presence of copies of the short polymorphism. At its core stands the assumption that, despite the shared tendency toward social impairments, (for a classical discussion regarding this profile in depression and the potential role of the short polymorphism of the 5-HTTLPR, see: [26]; for a similar discussion regarding antisocial disorder, see: [4]), MDD and ASPD tend toward opposite affective styles.

While individuals suffering from MDD are notably defensive and characterized by a general sensation of fear (which ties MDD to anxiety [30]), carriers of antisocial disorder re notably offensive and characterized by a decreased sense of danger. In terms of the relation with stressors, MDD is characterized by hyperresponsivity to mental and biological to stimuli of negative valence, while ASPD is characterized by the opposite pattern. For a discussion of this conclusion, several times replicated, see: [31]). Carriers of ASPD also differentiate themselves phenomenologically from carriers of the MDD through the cognitive tendency to believe that they are correct in their beliefs and attitudes and, paradigmatically, throu gh lower concerns about the consequences of their acts [3].

Moreover, it is emblematic that the two main molecular pathways in which antidepressant medications act respectively involve the inhibition of selective serotonin reuptake (an effect that is opposed to the one that is favored by the presence of copies of the short polymorphism) and inhibition of the enzymatic activation of the MAO-A (an effect that resembles the presence of copies of the short variation of the MAO-A gene). In the figure below, I present the main biological dimensions of interest to the understanding of this dichotomy. These figures and analyses were generated for the occasion, with the use of several bioinformatics tools.

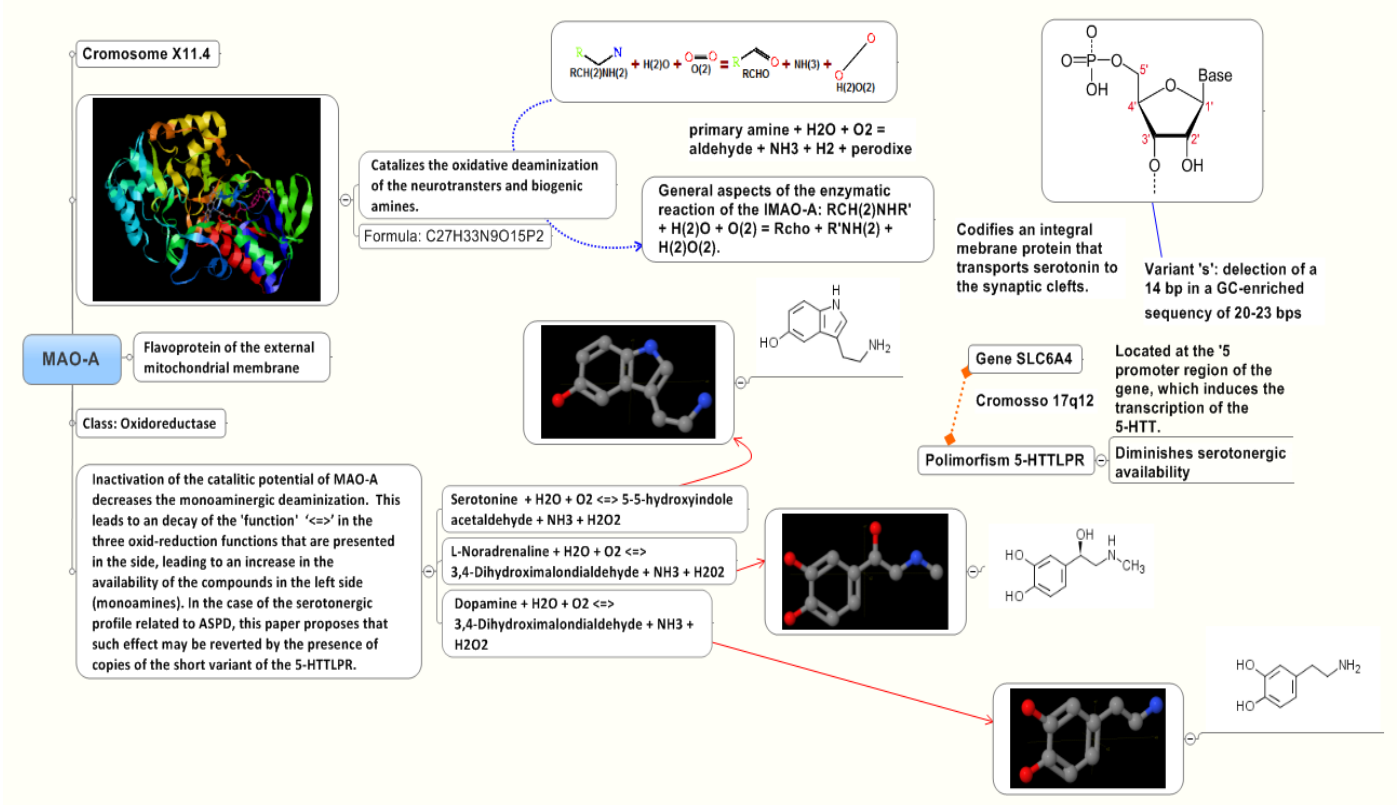

Figure 1: The neurobiological dimensions of ASPD under focus

From this complex panorama emerges the conclusion that under the same nature-nurture paradigm, a genetic risk factor that has been traditionally associated to hyporesponsive copying and cognitive style represents one of the additive genetic risk factors to an offensive and hyperresponsive condition, whose main genetic association is represented by a polymorphism that induces a state of enzymatic hypofunction, which medications to the other disorder try to mirror. This is the essence of the etiological paradox of the genetic vulnerability to antisocial personality disorder that I propose to shed light into.

3. A POSSIBLE SOLUTION TO THE ETIOLOGICAL PARADOX OF ANTISOCIAL PERSONALITY DISORDER

As it applies to most complex nature/nurture interactions, the number and roles of the variables involved in this case may surpass by much the present framework, as much as the canonical perspectives in behavioral genetics of the current days. In that sense, it would be imprudent to propose solutions to the identified paradox, without emphasizing their limited, historically dated scope, imposed by the necessity to discuss a legit problem, using scarce tools and information.

In this context, the apparent dichotomy that emerges in relation to the presence of copies of these two dysfunctional genetic variations in ASPD (short variations of the MAO-A and 5-HTT genes), is made gradually understandable, as we consider that:

1. contrary to what is suggested by several studies (i.e., [32]), the functionality of the serotonergic neurotransmission cannot be thought of solely in terms of net 5-HT levels in the brain or in the serum, but is intrinsically dependent on the action of the transporters that are codified by the SLC6A4, as illustrated in the figure below. In spite of the lack of studies addressing this specific point, the present hypothesis proposes that, within the complex postsynaptic monoaminergic circuitry (above the brainstem sites, where the monoamines are synthesized), the general increase of the 5-HT levels caused by the MAO-A hypofunction does not lead to serotonergic hyperfunction (or even normal function), since effective neurotransmission is dependent on the biding capacities of the biochemical transporters.

The core point to be considered herein is the existence of a convergent dimension on the level of the neurobiological vulnerabilities to both disorders. This dimension is important to the proper understanding of ASPD's structure, regardless of the decreased serotonergic degradation, imposed by MAO-A hypofunction. That said, it is important to go beyond the naive premise that the increase in vulnerability to major

depression represented by the presence of copies of the polymorphic short variation of the SLC6A4 represents a direct effect of the serotonergic hypofunction. Current views of the nature-nurture structure of depression suggest that it is much more appropriately seem as a complex byproduct of an intensification of the vulnerability to a wide range of deleterious personality manifestations, which can be more specifically defined under the concept of neuroticism ([33, 34]; that is, of a personality style linked to negative emotional states and acute conflictive interactions.

In essence, the emerging idea is that, triggered by life-events, the presence of copies of the short variant of the 5-HTTLPR increases the chances of looping low mood and stressful situations, and of converting its mental effects into insults to the nervous system [35, 36], in light of broader personality tendencies - which place the individual in the "at risk" group for several affective disorders - and regardless of the consolidation of any full-blown nosographic unit.

This assumption, that was already behind Caspi's classical study on proneness to depression [21], reveals a perspective that is frequently overlooked: *per se* the presence of copies of the short variant of the 5-HTTLPR does not increase the specific vulnerability to major depression, but rather the vulnerability to the effects of stress on the determination of the predominant affective style and the brain's morphology (i.e., bilateral amygdala enlargement, prefrontal hypofunction; see: [37]). The clinical condition that has been at the core of this debate - major depression - is one that emerges from the additive effects of this proneness and several other behavioral and biological variables that precisely differentiate it from APSD, and several other disorders (for confirmatory meta-analyses, regarding other disorders, see: [38-40]).

The current hypothesis points to the existence of a etiological bifurcation, in face of which, victims of early stress that carry the short variant of the 5-HTTLPR (and, thus, a tendency to develop negative interactions) will become potentially vulnerable to opposite affective styles, during the adolescence and early adulthood (for data on depression: [41]; for data on antisocial disorder [42]). That is our starting point to the deeper understanding of the phenomenological structure of ASPD.

It is suggestive from this point of view that the environment where the consolidation of the subject's personality takes place represents a fundamental piece in this puzzle. Not so ever, what the current hypothesis emphasizes is the role of the polymorphic risk factors. In that vein, it is important to reapply the argument and accepting the theoretical challenges imposed by the truism that it would be incorrect to assume that the effects of the MAO-A dysfunction could possibly overcome those of the 5-HTTLPR dysfunction, or the other way around.

Starting from mutually shared neurotic tendencies, there are important endophenotipic, mental, and behavioral aspects emerging from the systemic central and peripheral neurochemical balance that is defined by the neurochemical balance created by the association of low serotonergic neurotransmission with low overall monoaminergic degradation. For instance, an important and yet overlooked neurochemical difference between stress-related conditions and depression is that "induced stress experiments on mammals reveal that chronic stress leads to central noradrenergic (NA) depletion and increased adrenergic (Ad) and noradrenergic serine levels, much in the same way that it occurs in cases of major depression. Nonetheless, while the ratio NA/Ad is increased in the latter, it is decreased in former experimental conditions" [43]; p. 35).

Decreased MAO-A activity leads to an enhanced adrenergic profile, due to a decrease in the degradation of norepinephrine; and one should consider that the vulnerability to ASPD involves an important autonomic component, which probably bias the conflictive tendencies that are common to neuroticism toward a more offensive style, in a manner that is not seem in MDD (additional endorsement to this hypothesis comes from association studies pointing to that MAO-A hyperfunctional polymorphisms, represent risk factors to MDD [44]).

Adding to this difference, the less functional variants of the MAO-A gene also lead to increased dopaminergic profiles, which boost the activation of reward circuits. In this context, the excess of available dopamine favors potentially prepotent tendencies toward rewards that can easily be translated into goals such as winning conflictive interactions, satisfying impulsive tendencies toward immediate goals, and avoiding regret . Hyperactivation of reward circuitry are also involved in higher tendencies toward drug abuse and addiction [45]), which are intimately related to higher antisocial tendencies [46].

Drug abuse & addiction places the subject in a context where antisocial conducts are acutely stimulated, both in terms of the economic pressures that come from consumption and in terms of the of the dissemination of social interaction models, where delinquent behavior is valorized (for a discussion, regarding the Brazilian population of young incarcerated offenders, see: [47]). Prefrontal hypofunction (specially right ventral-medial and orbital-frontal) represents one of the most remarkable neurobiological basis of the inability to inhibit impulsive tendencies [48], and thus of avoiding inconsequent behaviors.

Altogether, cases of ASPD involve complex neurobiological facilitations of tendencies that converge an antisocial profile, which has evident links to the social-economic context, where early stress, violent disputes, and drug abuse & addiction emerge as natural consequences of social policies that do not carry the premise that it would be strategic to prevent social-affective disorders, before the at risk individuals convert their existences from conflictive to destructive.

CONCLUSION AND SUGGESTIONS FOR FURTHER STUDIES

This article described an apparent paradox related to the mental (affective style) and behavioral (flight or fight) styles that emerge from the presence of two genetic risk

factors that are currently associated to antisocial disorder; and then presented a hypothesis to ease the understanding of such puzzle, light of knowledge regarding the neurobiological and phenomenological basis of depression.

As proposed, the mental and behavioral profile of individuals at risk (we considered the cases of those who carry both variants, without disregarding the heterogeneity of the cases) should be understood in the following manner: serotonergic hypofunction increases the rates of conflictive tendencies and the possibility of looping them into a personality style & into insults to the nervous system. Among other effects that are less important to the understanding of the current scenario, MAO-A hypofunction intensifies peripheral stress levels (adrenergic) and the activation of dopaminergic reward circuits, which converge into higher impulsivity, aggressiveness, prepotent tendencies, and vulnerability to drug abuse & addiction - a group of mental and behavioral tendencies that tend to cluster together in the personality of most individuals at risk of developing antisocial personality disorder.

To the extent that this hypothesis is valid, it is expected that the presence of copies of the short variant of the 5-HTTLPR exert an additive effect in the consolidation of the personality at risk, by the introduction of higher conflictive tendencies. New studies are needed to evaluate this hypothesis and increase our capacity to distinguish these profiles and develop social & clinical proposals to properly deal with them, as much as to understand & deal with the several other ASPD profiles that are probably waiting to be uncover.

Conflicts of Interest: None
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